

Prescriber Update

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FROM THE EDITOR

Prescribers – don't miss out!

If you or your fellow prescribers are not receiving these hard-copy issues of *Prescriber Update* by mail, then forward your name and postal address to the Editor (contact details on page 19). There is no cost for prescribers to join the *Prescriber Update* mailing list and your details will be used only for this purpose.

Be the first to know

Prescribers and pharmacists can subscribe to receive e-mail notification of new *Prescriber Update* articles and other safety-related medicine information issued by Medsafe. To subscribe to this free service, go to www.medsafe.govt.nz/profs.htm and click on where it says "Click here to subscribe to Prescriber Update Previews" in the centre of the screen. Complete and submit your details to receive e-mails with hyperlinks to new articles (and other relevant information) published on the Medsafe web site.

Salamol inhalers – clean once weekly

There have been reports of Salamol® (salbutamol) inhalers blocking. As a result, Medsafe is testing the devices. In the interim, please remind patients of the importance of cleaning the inhaler devices **once every week**. Instructions are enclosed with each inhaler.

Media stories – separating fact from fiction

For an objective critique of media news stories relating to medical issues, the following web sites may be useful for health professionals:

- www.nelh.nhs.uk/hth/archive.asp (National Health Service, United Kingdom)
- www.mediadoctor.org.au (Newcastle Institute of Public Health, Australia)

'Off-label' use of medicines

Medsafe recognises that the unapproved (or 'off-label') use of medicines is sometimes appropriate. In such instances, section 25 of the *Medicines Act 1981* allows a registered medical practitioner to "procure the sale or supply of any medicine" (approved or unapproved) for a particular patient in his or her care. "Procure the sale or supply" refers to obtaining the medicine through the usual channels such as a pharmacy or a pharmaceutical company, and it also permits the practitioner to use other means of obtaining a medicine such as importation. Section 25 is intended to allow medical practitioners to either obtain unapproved medicines, or to use medicines for an unapproved indication, for the treatment of a particular patient in the care of that or another practitioner.

There are limitations to this authority embedded in the *Code of Health and Disability Services Consumers' Rights 1996*. Unapproved use of medicines must comply with this Code, which states that the patient has the right to treatment of an appropriate ethical and professional standard, and the doctor has the responsibility of ensuring that the treatment, whether approved or unapproved, meets this standard. The patient also has the right to be fully informed. If the use of a medicine is unapproved, the patient should be so advised and the doctor should be frank about the level of evidence for the medicine's efficacy as well as any safety concerns. The doctor must fully discuss both the risks and benefits with the patient/parent, and in appropriate circumstances this may lead to the use of a medicine with informed consent. For more information on unapproved use of medicines see www.medsafe.govt.nz/Profs/RIss/unapp.htm

Free resources available

- **Prescribing Medicines in Pregnancy** booklet (4th edition)
- Patient information leaflet on **oral contraceptives and blood clots** (March 2002 update)
- Consumer Medicine Information (**CMI**) poster.

To order copies of any of these resources, at no charge, contact Wickliffe: phone 04 496 2277, fax 03 479 0979, email pubs@moh.govt.nz or post an order to the Ministry of Health, c/- Wickliffe Ltd. PO Box 932, Dunedin.

Key to *Prescriber Update* articles

To assist readers in knowing the origin of articles published by Medsafe, the symbols below will appear next to the article title, where applicable.



Adverse Drug Reaction Update

articles are written in response to adverse reaction reports lodged with the Centre for Adverse Reactions Monitoring (CARM) and material in the international literature. These articles may also be written to alert prescribers and pharmacists to potential problems with medicines.



MARC Prescribing Advice articles are recommendations from the Medicines Adverse Reactions

Committee (MARC) in response to medicine safety issues and overseas experiences.

Not music to everyone's ears!

A 78-year-old male developed musical hallucinations whilst taking voriconazole for antifungal prophylaxis as part of a hospital-based experimental protocol. The hallucinations were solely of Christmas music, had commenced on the second day of treatment and persisted for the next 5 days of taking voriconazole. The music was so realistic that the patient wrote a letter to the hospital complaining of the constant music. He was able to list the songs that he heard including the Christmas carol "Do you hear what I hear?". The patient had no previous psychiatric history; mental status examination revealed normal cognitive functioning and no evidence of delirium. Due to the close temporal association between initiation of voriconazole and onset of the musical hallucinations, voriconazole was implicated as being the most likely cause and was discontinued. Three days later the patient reported complete cessation of the music.¹

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PRESCRIBING RESTRICTIONS FOR ALL COX-2 INHIBITORS



The following fax was distributed to all GP surgeries, hospitals and pharmacies on 29 April 2005. It was also published on the Medsafe web site: www.medsafe.govt.nz/hot/DHCPFaxApril05.htm

29 April 2005

Important information for doctors and pharmacists:

Prescribing restrictions for all COX-2 inhibitors

After evaluation of the available data, and consideration of submissions from patients and health professionals, the Medicines Adverse Reactions Committee (MARC) has recommended that the COX-2 inhibitors celecoxib (Celebrex), etoricoxib (Arcoxia), lumiracoxib (Prexige), meloxicam (Mobic) and parecoxib (Dynastat) should not be withdrawn from the New Zealand market. However, the MARC considers that an increase in cardiovascular risk is a class effect for all COX-2 inhibitors. Therefore, the MARC have made the following recommendations to Medsafe in order to appropriately manage this increase in risk:

- COX-2 inhibitors should be contraindicated:
 - In patients who have previously had a myocardial infarction or stroke
 - Peri-operatively in patients undergoing cardiac or vascular surgery
 - Peri-operatively in patients at high risk of cardiovascular disease undergoing major surgery.
- Etoricoxib should be contraindicated in patients with poorly controlled hypertension.
- COX-2 inhibitors should not be used unless alternative therapies have been used and found to lack analgesic efficacy or to have unacceptable adverse effects in the individual patient.
- COX-2 inhibitors should be commenced at and titrated to the lowest effective dose for pain control. Treatment should be limited to the shortest possible duration.
- Patients should be reviewed after two weeks and the COX-2 inhibitor discontinued if there is a lack of therapeutic benefit. Patients requiring long-term therapy should be reviewed every three months to assess their ongoing need for treatment and the development of any new cardiovascular risk factors.
- Prescribers should be aware that COX-2 inhibitors may exacerbate pre-existing hypertension, cardiac failure or oedema.
- Aspirin should not be discontinued in patients requiring aspirin for cardiovascular prophylaxis. However, prescribers should be aware that there is no evidence that the use of aspirin mitigates the increased cardiovascular risk associated with COX-2 inhibitors. In addition, aspirin use has been shown to negate most of the gastrointestinal advantages associated with COX-2 inhibitors.
- Prescribers must ensure that all patients at high risk of cardiovascular disease are informed that use of a COX-2 inhibitor might increase their risk of having a heart attack or stroke.
- It is important that discussions regarding peri-operative use of COX-2 inhibitors are undertaken prior to surgery.

Medsafe is in the process of implementing the MARC's recommendations. Medsafe has also asked the COX-2 inhibitor product sponsors to continue with the voluntary moratorium on Direct-to-Consumer and professional advertising.

In light of the voluntary withdrawal of valdecoxib (Bextra) by Pfizer on 11 April 2005, Medsafe and the MARC are reviewing further safety information on this medicine. A decision regarding the most appropriate strategy to manage the risks associated with the use of Bextra is likely to be made after the next MARC meeting on 9 June 2005.

June 2005 Progress update:

Medsafe is currently working with the sponsors of all the COX-2 inhibitors to update the data sheets to reflect the above MARC recommendations.

Further information is available on the Medsafe web site:

- Minutes of the 15 March 2005 MARC meeting: www.medsafe.govt.nz/Profs/adverse.htm
- Media statement (29 April 2005): www.medsafe.govt.nz/hot/MediaContents.htm

Disseminated by Medsafe

Medsafe Pharmacovigilance Team

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in February 2005.

Amiodarone has been associated with serious adverse reactions affecting the eyes, lungs, liver, heart and thyroid gland. Prescribers should be vigilant for these unwanted effects, and are reminded of the importance of intensive clinical monitoring of patients receiving amiodarone. Patients should also be informed of the warning symptoms of amiodarone toxicities and to seek immediate medical advice should these occur.

Amiodarone indicated for treatment of cardiac rhythm disorders

Amiodarone hydrochloride (Cordarone X[®], Aratac[®]) is a Class III antiarrhythmic agent approved in New Zealand for the treatment of tachyarrhythmias associated with Wolff-Parkinson-White syndrome; and paroxysmal tachyarrhythmias, atrial flutter and atrial fibrillation when other agents cannot be used.^{1,2} Amiodarone acts by reducing membrane excitability in myocardial tissue, primarily by prolonging the duration of the action potential and subsequent refractory period of atrial, nodal and ventricular tissue.³ The long half-life of amiodarone (approximately 50 days) may contribute to the slow resolution of adverse effects following cessation of the medicine.⁴ The most serious potential unwanted effect of amiodarone is pulmonary toxicity (with a fatality rate of about 10%⁵); other harmful effects include visual disturbances as well as hepatic, cardiac and thyroid toxicities.^{1,2,4-6}

NZ reports include serious adverse reactions associated with amiodarone

The Centre for Adverse Reactions Monitoring has received 340 adverse reaction reports associated with amiodarone therapy, up to the end of December 2004. These reports include the following serious adverse reactions (number of reported cases is given in brackets):

Visual Disturbances

Eye problems including keratitis (13), corneal ulceration (1), eye pain (1), corneal oedema (1), optic neuritis (1), retinal disorder (1) and scotoma (1). There have also been 19 reports of corneal deposits and 10 reports of abnormal vision.

Pulmonary Toxicity

Serious pulmonary reactions include pulmonary fibrosis (10), pneumonitis (8), pneumonia (5), alveolitis (3), pleural effusion (2), interstitial lung disease (2), pulmonary oedema (1) and respiratory failure (1).

Hepatotoxicity

Cases of serious liver toxicity including cirrhosis (2), necrosis (2), hepatitis (3) and hepatocellular damage (6). There have been 15 reports of liver enzyme disturbance.

Cardiac Toxicity

There have been a number of adverse reactions affecting the cardiovascular system including arrhythmias (10), hypotension (10), hypertension (4), torsades de pointes (2), cardiac arrest (1), cardiac failure (2), pulmonary embolism (1), sudden death (2), and several reports of aggravation of chest pain.

Thyroid Toxicity

Thyroid disturbances include reports of hypothyroidism (12), thyrotoxicosis (1) and thyroid disorder (4).

Baseline assessment and ongoing monitoring is recommended

Before a patient is commenced on amiodarone therapy, prescribers should ensure that the following baseline assessments are completed:^{1,2,4-6}

- pulmonary function assessment (including chest X-ray)
- ECG and serum potassium levels
- liver function tests

- thyroid function tests
- ophthalmological examination if there is pre-existing visual impairment.

Many of the adverse effects of amiodarone are related to dosage and duration of use.^{4,6} Therefore, in addition to using the lowest possible dose, it is recommended that patients on long-term amiodarone therapy should regularly undergo the following monitoring:^{1,2,4-6}

- lung function assessment (including six-monthly chest x-ray)
- ECG and serum potassium levels (ideally every 6-12 months)
- liver function tests (six-monthly)
- thyroid function tests (six-monthly)
- annual eye examinations (e.g. slit lamp biomicroscopy, visual acuity, fundoscopy) but more immediately or frequently if visual changes occur.

Expect the unexpected ... as well as the expected

Amiodarone can cause hyperthyroidism and hypothyroidism.^{1,2,4-6} The risk of amiodarone-induced hyperthyroidism may remain present for at least three months after the medicine has been stopped. Consequently, thyroid function should continue to be monitored for several months following discontinuation of amiodarone.^{1,2,4} It is worth noting that amiodarone can affect thyroid function test results, therefore, serum TSH level should be measured when thyroid disturbance is suspected.^{1,2} Furthermore, if new signs of arrhythmia appear, consider hyperthyroidism as the potential cause.⁵

Corneal deposits develop in almost all patients taking amiodarone but are generally considered benign.^{1,2,4} However, all patients should promptly receive an ophthalmological examination (including fundoscopy) if visual symptoms such as blurred, or decreased, vision develop or worsen.^{1,2,5}

Photosensitivity is another common side effect associated with amiodarone, and may persist for some months after treatment discontinuation. The risk of photosensitivity can be minimised by advising patients to avoid sun exposure as much as practical and to use protective measures (e.g. sunscreen) during, and for at least three months after stopping, amiodarone therapy.^{1,2,4}

Specialist, GP and patient co-ordination facilitates monitoring

Amiodarone is fully subsidised when prescribed by, or on the recommendation of, a specialist.⁷ While a specialist is likely to initiate amiodarone therapy, the patient's general practitioner (GP) may well prescribe maintenance therapy. Therefore, it is useful to ensure that the lead carer is clearly identified. Liaison between specialists and GPs is important in ensuring that patient monitoring is carried out, and that adverse effects are appropriately managed.⁴ In addition, patients should be informed of potential symptoms of amiodarone toxicity and encouraged to promptly contact their doctor if symptoms develop.

Competing interests (authors): none declared.

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SYNCOPE AND DEMENTIA TREATMENT – CATCHING THE FALLS



Medsafe Pharmacovigilance Team

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in June 2005.

Acetylcholinesterase inhibitors, used to treat dementia of the Alzheimer-type, are associated with syncopal adverse events. This risk can be minimised by prudent management including gradual dose increments and obtaining a pre-treatment ECG. Prescribers are reminded that alternative causes of syncope should be considered including dementia and other disease states. Concurrent medicines can also increase the risk of syncope in dementia patients on acetylcholinesterase inhibitors.

AChEIs help improve cognitive function in dementia

Acetylcholinesterase inhibitors (AChEIs) are indicated for the treatment of the symptoms of mild to moderately severe dementia of the Alzheimer-type. The AChEIs currently available in New Zealand are donepezil (Aricept®), galantamine (Reminyl®), memantine (Ebixa®) and rivastigmine (Exelon®). These medicines work by inhibiting the breakdown of acetylcholinesterase in the synapses, thus increasing the amount of acetylcholine available at post-synaptic neurons. The resultant increase in central cholinergic neuronal activity is thought to mediate benefits in cognitive and behavioural functions in patients with dementia.^{1,2} The goal of treatment in patients with Alzheimer's disease is stabilisation of cognitive, behavioural and functional status; at best, some increase in cognitive function may be achieved.¹

The adverse reactions of the AChEIs are generally mild and transient, and can be limited by introducing dose increases slowly. Gastrointestinal events such as nausea, vomiting and diarrhoea are most common. These can be minimised by taking doses with food, as well as ensuring adequate hydration and gradual dose increments.^{1,2}

Post-marketing reports of syncope with AChEIs

Internationally, there have been several published reports of syncope occurring in patients taking donepezil.³⁻⁷ In New Zealand, adverse reaction reports of syncope associated with AChEIs include the following:

- A 77-year-old female, who had been on donepezil for more than five years, experienced syncope along with somnolence, dysphasia and dehydration.
- A 73-year-old woman prescribed rivastigmine had a syncopal episode and a non-specified arrhythmia within a month of starting treatment.
- A 63-year-old woman taking donepezil experienced syncope and bradycardia. It was not known how long she had been on donepezil.

Syncope can also be due to other causes

In patients with dementia, syncope can be caused by a number of factors including use of AChEIs, the dementia itself or other not necessarily related disease states, making it difficult to identify the causal factor. Syncope, repeated falls and transient loss of consciousness may be associated with all forms of dementia, but are more commonly associated with specific sub-types, e.g. dementia with Lewy bodies.⁸ There are a number of other pathologies that may be potential causes of syncope. Orthostatic hypotension may be responsible for syncope in up to 30% of the elderly; co-administration of antihypertensives may be a contributor in these patients. Carotid sinus hypersensitivity, cardiac arrhythmia and seizures should also be considered as differential diagnoses when determining the likely cause of syncope.⁹ Age-related falls in patients with dementia are common, and may be related to the high prevalence of orthostatic hypotension and carotid sinus

hypersensitivity in patients with Alzheimer's disease and dementia with Lewy bodies.¹⁰

Syncope is known to occur with memantine (in up to 2% of patients), donepezil (2%), rivastigmine (0.1-1%) and galantamine (0.01-0.1%).¹¹⁻¹⁴ Other cardiovascular adverse events of the AChEIs include bradycardia and dizziness, mainly mediated by a vago-tonic effect on the heart due to muscarinic stimulation.^{2,10} Consequently, caution is advised when prescribing AChEIs to patients with sick sinus syndrome, or other supraventricular cardiac conduction conditions, such as sinoatrial or atrioventricular block.¹¹⁻¹⁴ Obtaining an ECG prior to starting AChEIs in any patient would be a prudent measure to reduce the risk of syncope, and will assist in excluding or identifying other causes of syncope.

Interactions may increase risk of syncope

An additional risk factor for syncopal episodes with AChEIs is interactions with other medicines.^{1,2} In particular, concurrent medicines with bradycardic or cholinergic effects should be used with caution, as they may further increase the risk of syncope; such medicines include beta-blockers, digoxin, neostigmine, succinylcholine and pyridostigmine.¹²⁻¹⁴ There is also a potential interaction between donepezil and inhibitors of the cytochrome P450 isoenzymes 3A4 or 2D6 (e.g. ketoconazole, itraconazole, erythromycin, quinidine and fluoxetine), resulting in increased blood concentrations of donepezil;¹² this could increase the risk of syncope.

The risk of AChEI-induced syncope can be minimised by gradual upward dose titration until the maintenance dose is reached. Similarly, if treatment is interrupted for longer than several days, it should be re-initiated with the lowest daily dose.¹²⁻¹⁴ When adding in other medicines, be aware of the potential for increased syncopal risk. Should syncopal episodes persist, consider stopping or reducing either the dose of the AChEI or any concurrent medicines that may be compounding the risk of syncope.

Competing interests (authors): none declared.

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Medsafe Pharmacovigilance Team

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Prescribers are reminded that thioridazine is a third-line antipsychotic agent and should only be prescribed in patients for whom the therapeutic benefits clearly outweigh the risk of arrhythmia from QT-prolongation.

Thioridazine (Aldazine[®], Melleril^{®*}) increases the risk of arrhythmia from QT-prolongation. Consequently, the Medicines Adverse Reactions Committee (MARC) recommended changes to how thioridazine is prescribed in New Zealand. The following advice was issued in June 2001 (see www.medsafe.govt.nz/profs/PUarticles/thioridazine.htm), which the MARC would like to reiterate.

Thioridazine is contraindicated in the following circumstances, all of which are risk factors for arrhythmia:

- use with medicines which inhibit the metabolism of thioridazine (cimetidine, most antidepressants, pindolol, propranolol)
- use with medicines which prolong the QT-interval (some antiarrhythmics, most antipsychotics, cisapride)
- use in patients with predisposing factors for arrhythmia or pre-existing QT-prolongation ($QT_c \geq 500\text{ms}$).

Thioridazine should be initiated only by a specialist and only as third-line therapy. In addition, the following precautions should be observed for new patients:

- assess for risk factors for arrhythmia
- check the QT_c -interval and serum potassium
- use the minimum effective dose
- observe a maximum of 200mg daily ordinarily
- use dosages above 200mg daily up to a maximum of 600mg daily only under specialist supervision and only with QT_c -interval monitoring following each increase.

For all patients currently taking thioridazine:

- assess for risk factors for arrhythmia
- check the QT_c -interval and serum potassium
- doses above 200mg daily require review by a specialist
- reduce the dose if QT_c -interval $\geq 500\text{ms}$
- withdraw thioridazine if QT_c -interval is persistently $\geq 500\text{ms}$, or in the presence of any contraindication.

Any children taking thioridazine should also have their therapy reviewed by a specialist. If thioridazine discontinuation is necessary, gradually reduce the dose over a period of one month and concurrently introduce alternative medication. Specialist supervision may be advisable for the withdrawal process.

Competing interests (authors): none declared.

* Novartis has advised that from 1 July 2005 supplies of Melleril will no longer be available

ACNE, ISOTRETINOIN AND DEPRESSION

*Drug and Therapeutics Bulletin** 2003;41:76-78, reprinted with kind permission from Which? Ltd, 2 Marylebone Road, London NW1 4DF, United Kingdom.

At any one time, most 16–18-year-olds and up to half of adults have acne.¹ In 60% of all teenagers, the condition will be sufficiently severe for them to self-treat or seek medical advice.² Up to half of 12–20-year-olds with acne develop psychological or social problems.³ Oral isotretinoin, which is used for the treatment of severe acne,⁴ might be expected to improve psychological functioning.^{5,6} However, there have been suggestions that the drug itself might cause depression and suicide.⁷ Here we consider these concerns, and the implications for the use of isotretinoin when managing patients of all ages.

Background

Most patients with mild acne (i.e. few to several papules or pustules, but no nodules/cysts) or moderate acne (several to many papules and pustules, plus few to several nodules/cysts) manage themselves or are treated in primary care with topical antimicrobials, keratolytics or retinoids and/or oral antibacterials.^{8,9} Oral isotretinoin is an option for the 0.6–1.4% of young adults with severe acne (numerous and/or extensive papules and pustules, plus many nodules/cysts, possibly also with pitting or scarring).⁸

What is isotretinoin?

Isotretinoin (13-*cis* retinoic acid) is a derivative of vitamin A. Following oral administration, it is converted to all-*trans* retinoic acid within target cells (sebocytes) and this metabolite suppresses sebaceous gland activity.¹⁰ Isotretinoin was originally licensed for use in the USA as Accutane in 1982, and in the UK it is currently available from Roche (as Roaccutane[®]) and from Schering Health (as non-proprietary isotretinoin). [New Zealand brands of isotretinoin include Isotane[®] and Oratane[®]]

Clinical efficacy

Isotretinoin, which is recommended as a 12–16-week course,¹¹ can be highly effective in moderate to severe acne when other treatments have failed. A meta-analysis of three trials, including a total of 426 patients, suggested isotretinoin cured around 85% of patients after an average treatment course of 4 months.¹² The optimal dose was 1mg/kg/day with a maximum cumulative dose of 120mg/kg. After stopping the drug, about 1 in 5 patients relapsed.

Established unwanted effects

Isotretinoin has many unwanted effects. It is teratogenic, causes cheilitis (inflammation of the lips), dry eyes and dry nasal mucosa, and may cause minor nosebleeds, dry skin and photosensitivity, muscle aches and pains and fatigue, visual disturbances, thinning of scalp hair, and a transient rise in liver transaminases and serum triglyceride concentrations.¹¹ Due to its potential toxicity, isotretinoin is only licenced [in the UK] for prescription by, or under the supervision of, consultant dermatologists,¹¹ and

* About Drug and Therapeutics Bulletin

Drug and Therapeutics Bulletin (DTB) is a monthly publication giving rigorous and independent evaluations of, and practical advice on, individual treatments and the overall management of disease. It is published by Which? in the UK, carries no advertising and is wholly independent of industry, Government, regulatory authorities and the medical establishment.

DTB articles are based on a synthesis of evidence (in particular from randomised controlled clinical trials), with opinions from a wide range of commentators. Before publication, articles are circulated several times, typically to up to 100 individuals/organisations, including clinical specialists and generalists, patient advocates and other experts, regulators and the Government. The conclusion of each article reflects careful assessment by a team of in-house editors and aims to provide the best available advice on treatment.

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it is therefore almost exclusively dispensed by hospital pharmacies. Some specified community pharmacies [in the UK] may supply it after authorisation by a dermatologist for specific patients. [In New Zealand, isotretinoin should only be prescribed by physicians who are experienced in the use of systemic retinoids, preferably dermatologists.^A The Isotane brand is fully funded when prescribed by a dermatologist and dispensed by a hospital or community pharmacy contracted to dispense as a hospital pharmacy.^B]

What about depression?

Scattered case reports of mood change, depression and suicide in patients taking isotretinoin have appeared since the drug was first licensed.¹³ However, establishing whether isotretinoin causes or aggravates depression is complicated by the high background prevalence of psychiatric illness among adolescents in general (estimated at over 25% in one study¹⁴) and among patients with acne (over 50% in a study of dermatology outpatients with a mean age of 24 years¹⁵). Published studies have been unable to adjust fully for these potentially confounding factors.

Collated evidence from case reports

A review of spontaneous reports to the USA Food and Drug Administration (FDA) between 1982 and 2000 included 431 cases of depression, suicidal ideation, suicide attempts or suicide among patients (aged 13–32 years) treated with isotretinoin (0.5–2.5mg/kg/day).⁷ Some of these case reports fulfilled criteria suggesting a causal association: depression beginning or worsening after starting the drug, improvement in symptoms after withdrawal of the drug, and worsening of symptoms when the drug was reintroduced. However, it is not obvious how isotretinoin could cause such effects, particularly where depression or suicide occurs months after stopping the drug. The reports included 37 patients who committed suicide, of whom 24 were still taking the drug (median duration of treatment 3 months) and 13 had stopped (suicide occurred a median of 2.5 months after stopping isotretinoin). In all, 22% of these patients had a history of psychiatric illness and a further 40% had other factors that could have contributed to the suicide. Estimates of the numbers of suicides that could be expected in this

population in the absence of any predisposing effect of isotretinoin during the same time period varied between 6 (based on comparisons with other drugs monitored by the FDA) and 400 (using national incidence rates), compared with the 37 observed. The authors therefore suggested that the number of suicides reported did not exceed that predicted, although they acknowledged the possibility of considerable under-reporting of suicide to the FDA. The type of data collated in this study do not allow adjustment for the potentially confounding effect of acne itself in depression, suicidal ideation and possibly even suicide.^{15,16} However, at least some of the patients in this study were depressed in spite of improvements in their acne, raising the possibility that isotretinoin was a contributing factor in patients' mood disturbance.⁷

Epidemiological studies

A retrospective study separately analysed data from two primary care databases, one from Canada and the other from the UK, involving a total of 7,535 isotretinoin-users and 14,376 oral antibacterial-users (mostly aged 10–29 years) who had acne and for whom database information was available for at least 1 year after the first isotretinoin or antibacterial prescription.³ For neither group of patients were details given on the severity of the acne or on the treatment regimen used. This calls into question whether the two groups were directly comparable with regard to these criteria. These limitations must be borne in mind when considering the study results, which showed no increased risk of depression or psychosis among current isotretinoin-users compared with antibacterial-users (relative risk in Canada 1.2, 95% CI 0.9–1.76; in the UK 1.3, 95% CI 0.2–5.7). Also, the study did not have sufficient power to detect small differences in suicide rates. Additionally, it may not have identified all the patients with psychiatric disorders. For example, neither diagnostic interviews nor death-certificate data were used, and it is known that depression is under-diagnosed in primary care.^{17,18} Also, the number of patients on isotretinoin in the UK database may have been under-reported because the drug was prescribed by dermatologists whereas the database is limited to information from primary care.

A recent retrospective database study examined the records of 2,821 patients (aged 12–49 years) who had received both isotretinoin and antidepressant medication, to see if there was a greater likelihood of receiving the antidepressant after the isotretinoin rather than before (which could indicate a depression-provoking effect of isotretinoin).¹⁹ No significantly increased risk of receiving antidepressant after isotretinoin was found.

Prospective clinical studies of psychiatric events occurring in patients on isotretinoin have all involved small numbers of participants and lacked the power to identify or rule out an association. One example is a non-randomised study, in which 215 patients (aged 15–50 years), mostly with severe acne, were treated with isotretinoin, or antibacterials plus topical treatments.²⁰ Isotretinoin-users had more severe acne than those treated with antibacterials ($p < 0.001$). Five out of 174 patients taking isotretinoin (2.9%) complained of worsening mood and the drug was stopped. In 2 of these people, depression was thought not to be related to isotretinoin use because there were other psychosocial stressors present that could account for the symptoms, and these patients were continued on, or retreated with, isotretinoin without a recurrence of their depressed mood. Whether the symptoms in the other 3 people were due to isotretinoin or other factors was not clear. No depression was reported in the antibacterial group. The Beck Depression Inventory scores for the two groups did not differ significantly during the treatment period. The small number of people with depression and the difference in acne severity between the groups at the start of the study mean that the results are not robust and cannot be generalised to all patients.

Prospective randomised controlled studies would be needed to resolve whether isotretinoin makes depression more likely. Since any additional risk, if present, appears small, a trial would probably need several thousand patients in each of the two arms to detect an effect. Also, such trials would be difficult because withholding a drug of proven efficacy is likely to be ethically unacceptable and it would be difficult to blind participants due to the efficacy and unwanted effects of the drug.

Is isotretinoin overprescribed?

Dermatologists from several countries have recommended that, given isotretinoin's efficacy, the drug should also be prescribed to patients with mild or moderate acne.²¹ In keeping with this, a recent overview of the use of isotretinoin in the USA reported that isotretinoin is being used there for mild to moderate acne, increasing the population exposed to the drug and potentially to its unwanted effects.²²

Published advice on use

The current UK summary of product characteristics (SPC) from Roche (last revised January 2002) contains a warning that “Roaccutane may cause depression, psychotic symptoms and rarely suicide attempts and suicide. Particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression and referred for appropriate treatment if necessary.”²³ We have been advised by the company that the wording in the SPC is currently under review. [In New Zealand, the data sheet for Isotane states that “Depression, psychosis and rarely, suicidal ideation and attempts have been reported in patients treated with isotretinoin. Particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression and referred for appropriate treatment if necessary. Although no mechanism of action for these events has been established, discontinuation of therapy may be insufficient and further evaluation by a psychiatrist may be necessary.”^A]

Current guidelines from the British Association of Dermatologists conclude that whether isotretinoin can produce mood change is unproven.²⁴ However, they also include the following recommendations:

“A direct enquiry about previous psychiatric health should be made of all patients who are being considered for isotretinoin and the facts recorded fully in the notes. All patients, and their parents in the case of minors and adolescents, should be made aware of the potential for mood change in a realistic, non-judgemental way, and should be advised to ask their family and friends to comment

if such change should occur. Direct enquiry about psychological symptoms should be made at each clinic visit. If symptoms of depression or mood change do occur, then ideally, isotretinoin treatment should be discontinued. However, some patients, after discussion, may wish to continue with the drug because of the benefit to their skin. In this case, specialist psychiatric support should be obtained. If serious psychiatric illness is suspected, there should be an immediate referral to the psychiatric services.”

Healthcare professionals, and especially prescribers of isotretinoin, should be aware of the potential problems of depression among people with acne, and monitor for such symptoms. A history of depression is not an absolute contraindication to the use of isotretinoin, but the patient needs to be fully aware that symptoms might worsen on treatment. Any new episode of depression which occurs also requires close monitoring and treatment. All those in primary care directly involved in treating the patient (e.g. GP, nurse practitioner) need to be informed of any mood changes to allow a collaborative approach to management. If severe mood changes do occur while using the drug, specialist psychiatric support is advisable, with referrals being made urgently if there is an immediate concern about suicide. Less severe symptoms of depression could be managed by the GP or the community mental health team. Counselling and support may also be available from voluntary agencies (such as the UK Acne Support Group: www.m2w3.com/acne/). Psychiatric follow-up (by a specialist or in primary care) may need to be continued beyond the duration of isotretinoin therapy.

Conclusion

Oral isotretinoin is an effective treatment for patients with severe acne, but concerns have been raised that it may occasionally cause depression. However, retrospective studies have failed to demonstrate a clear relationship between isotretinoin and depression, and the few available prospective studies have lacked the power to identify such an association. Large randomised prospective studies of sufficiently long duration would be required to quantify any risks and weigh these against the benefits of isotretinoin. These studies would be difficult to carry out as they would inevitably deny some patients an accepted treatment, and blinding of treatment allocation would be difficult to achieve.

Clinicians should be alert to the high prevalence of depression among people with acne, and discuss these issues with patients and their carers before and during treatment. Because of its many unwanted effects, including a possible but unproven effect on mood, isotretinoin should ideally be reserved for patients with severe acne which has not responded to other therapies (and should only be prescribed by dermatologists). If depression or other mood change occurs, then, ideally, isotretinoin treatment should be discontinued. If treatment is continued, psychiatric support should be obtained. If serious psychiatric problems occur, the patient should be referred to a psychiatrist immediately.

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COUNTERFEIT MEDICINES – DON'T FAKE CONCERN

Medsafe Pharmacovigilance Team

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in June 2005.

Counterfeit medicines are a growing problem in many countries and are increasingly being supplied over the internet. As well as being deliberately fraudulent, there is the potential for harm with counterfeit medicines especially if treatment failure occurs. Health professionals and consumers should be vigilant for any unexpected effects or changes in medicines and report these to the appropriate authority.

A problem in both developed and undeveloped countries

Counterfeit medicines are becoming increasingly available worldwide. The number of investigations conducted by the Food and Drug Administration (FDA) in the USA has risen to more than 20 per year since 2000.¹ In 2004, there were 58 new cases investigated by the FDA.² Counterfeit prescription medicines found in the USA include Lipitor® (atorvastatin) and a brand of epoetin alpha (Procrit®),¹ as well as Viagra® (sildenafil) and Zyprexa® (olanzapine).³ In the UK, a counterfeit version of Cialis® (tadalafil) was discovered in 2004, following a consumer complaint of crumbling of the tablets.⁴ Counterfeit Reducil® (sibutramine) was also found in the UK last year, resulting in a patient-level recall of the counterfeit batch.⁵

A counterfeit medicine is one that is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can occur with both branded and generic medicines. Counterfeit medicines may include products with the correct ingredients but fake packaging, with the wrong ingredients, without active ingredients or with insufficient active ingredients.⁶ It is estimated that 5-7% of the global pharmaceutical market is counterfeit. In some Asian and African countries, this figure is closer to 40-50%.⁴

Awareness and vigilance are needed

While there have been no reported cases of counterfeit medicines entering the legitimate distribution chain in New Zealand, there are anecdotal reports of counterfeits appearing

amongst medicines being imported for personal use by consumers. This, along with the discovery of counterfeit prescription medicines in the UK and USA, illustrates that there is the potential for these products to come into this country.

It is worth noting there have been a number of herbal products and traditional Chinese medicines imported into New Zealand that have subsequently been found to contain undeclared prescription medicines such as corticosteroids and NSAIDs.⁷ Prescribers should be alert to this possibility when patients present with unusual or unexpected adverse (or even therapeutic) effects.

The presence of authenticity indicators, such as holograms and tamper-evident seals, on products is not always a reliable gauge as counterfeiters can replicate these. Detection often relies on awareness and vigilance by encouraging consumers to report any unusual features of their medicine. The following should be brought to the attention of the dispensing pharmacist or the pharmaceutical company who distributes/sponsors the medicine in New Zealand:³

- unusual taste or smell, particularly if different to the previously supplied product
- unexpected change in shape or colour of the medicine or its packaging
- inferior quality packaging materials
- poor quality or altered/absent printing on the packaging
- excessively repeated batch or lot numbers.

If health professionals notice any of the above, please notify the pharmaceutical company in the first instance and Medsafe secondly.

Patients should also be advised to inform prescribers of any unusual reactions, side effects or change in efficacy of the medicine. Similarly, prescribers should consider the possibility of a counterfeit medicine if the patient responds differently or unexpectedly, or if treatment failure occurs.³

Pharmacists requiring assurance about the authenticity of stock supplied to them should ask their wholesalers to confirm that they purchase directly from genuine manufacturers.⁸ Limiting the number of times a product changes hands between the pharmaceutical manufacturer and the end user helps to reduce the opportunities for counterfeit products to enter the supply chain.³

Beware of purchasing medicines on the internet

In some overseas cases, counterfeit medicines have been supplied over the internet.³ Use of the internet as a medium for selling counterfeit medicines is growing; it offers a global gateway (7 days a week, 24 hours a day) and it is easy to establish a convincing web site. If closed down, another site can be quickly created. Additionally, it can be difficult to identify and apprehend the people behind the web site.⁹

In New Zealand, it is illegal for consumers to be in possession of a prescription medicine unless it has been prescribed for them by a New Zealand-registered prescriber. Prescribers should take into account the medico-legal and ethical implications of providing consumers with a prescription for medicines ordered on the internet. Prescribers need to consider whether they are prepared to facilitate patient access to a medicine that has been delivered via an uncontrolled route of distribution (i.e. the internet) and whether they are able to reassure themselves that the product is of an appropriate safety, quality and efficacy, or that it actually contains the active ingredients required to treat the patient. It would additionally be prudent for prescribers to satisfy themselves that the medicine is appropriate for the patient's medical condition; also that the quantity of supply and dose are reasonable. Prescribers should also consider their legal liabilities and duty of care to patients if there are harmful or other consequences arising from the use of a medicine obtained over the internet

for which the prescriber provided a prescription. Prescribers who have queries about this should contact their medical indemnity organisation for advice. There are also guidelines provided by the New Zealand Medical Council (see www.mcnz.org.nz/portals/1/Guidance/Internet%20guidelines-revised2001.pdf).

As the risk of being supplied with a counterfeit is greater when medicines are obtained through the internet than from a New Zealand pharmacy, it would be reasonable to warn consumers against purchasing their medicines from internet sites based offshore. The Pharmaceutical Society of New Zealand (Inc) operates an accreditation programme to officially recognise New Zealand pharmacy sites that meet the prescribed professional standards for operating on the internet (see http://psnz.www0-w2k3.net24.net.nz/public/home/internet_accreditation/Intro.aspx).

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ADVERSE REACTIONS OF CURRENT CONCERN



The Medicines Adverse Reactions Committee (MARC) initiated the list of *adverse reactions of current concern* to bring particular medicine adverse reactions to the attention of prescribers. The intention is to encourage prescribers to report these reactions to the Centre for Adverse Reactions Monitoring (CARM) so that more information can be gathered, and further action taken if necessary. The reports provide a New Zealand perspective on emerging medicine safety issues.

As with any adverse reactions monitoring scheme, analysis can only be based on reports that are received. Prescribers are therefore encouraged to continue reporting adverse reactions to CARM so that the MARC can make the best possible recommendations based on information reflecting the New Zealand situation.

Regular amendments to the list of reactions are made either in response to adverse events reported in New Zealand or international pharmacovigilance issues.

Please report **all cases** of the following adverse reactions to: CARM, NZ Pharmacovigilance Centre, PO Box 913, Dunedin. Use the reporting form inside the back cover of *Prescriber Update*, or download the form from the CARM or Medsafe web sites: www.otago.ac.nz/carm or www.medsafe.govt.nz/Profs/adverse.htm

Medicine/s	Adverse reactions of current concern	Prescriber Update reference
Complementary and alternative medicines*	all adverse reactions	Vol.23(2), July 2002 & No.13, Oct 1996
Leflunomide	all adverse reactions	Vol.25(1), May 2004
SSRI antidepressants	severe agitation, severe restlessness/akathisia, and/or increased suicidality	Vol.23(3), Nov 2002

* includes herbal medicines, bee products, homoeopathic products, dietary supplements, minerals, and any other medicines containing animal or plant extracts.

About the IMMP

The purpose of the Intensive Medicines Monitoring Programme (IMMP) is to identify previously unrecognised adverse reactions to new medicines. It also develops adverse reaction profiles for these medicines, as well as measuring incidence and characterising reactions of clinical concern. In addition, the IMMP is able to identify any high-risk groups amongst the patients being treated. The results of IMMP findings are used to enhance the safe use of medicines.

Which medicines are monitored?

Medicines of a new class may be added to the IMMP so that unknown adverse effects can be identified as soon as possible. Medicines may also be included in the programme if they are similar to other medicines for which safety concerns exist.

Medicines currently monitored by the IMMP

Medicine	Proprietary name/s
Celecoxib*	Celebrex
Clozapine	Clozaril, Clopine
Etoricoxib*	Arcoxia
Levonorgestrel intrauterine system*	Mirena
Olanzapine	Zyprexa
Quetiapine	Seroquel
Risperidone	Risperdal
Rofecoxib*	Vioxx
Sibutramine*	Reductil
Valdecoxib	Bextra

* New patients are no longer being added to the cohorts for these medicines because sufficient numbers of patients have already been recruited. However, follow-up of existing patients is continuing so adverse event data are still being collected for these medicines.

What to report

Please report **all clinical events** in patients taking IMMP medicines, including:

- any suspected adverse reaction
- deaths (including cause if known)
- any new clinical events, even if minor or common
- accidents
- change in a pre-existing condition
- abnormal changes in laboratory test results
- possible interactions.

Where to report

Please report all adverse events occurring with IMMP medicines to: IMMP, NZ Pharmacovigilance Centre, PO Box 913, Dunedin. Use the reporting form inside the back cover of *Prescriber Update*, or download the form from either the NZ Pharmacovigilance Centre or Medsafe web sites: www.otago.ac.nz/carm or www.medsafe.govt.nz/Profes/adverse.htm

What to tell patients prescribed IMMP medicines

Please remember to tell patients that they have been prescribed a monitored medicine. This means the IMMP receives details of their prescriptions and that their doctor may be asked for clinical information on the patient's experience whilst taking this medicine. If possible, an explanatory IMMP leaflet should be given to the patient (available from the IMMP, NZ Pharmacovigilance Centre, PO Box 913, Dunedin).

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**Reporting form for Adverse Reactions
to Medicines, Vaccines and Devices
and all Clinical Events for IMMP**

PATIENT DETAILS

HP3442

Surname:		First Name/s:		NHI No:	
Address:		Date of Birth:		Sex:	
		Ethnicity:			

ALL MEDICINES IN USE *ASTERISK SUSPECT MEDICINE/S* Include over-the-counter (OTC) and alternative medicines

Medicine or Vaccine+batch no.	Daily Dose	Route	Date Started	Date Stopped	Reason for Use

DESCRIPTION OF ADVERSE REACTION OR EVENT

Date of onset: _____

Recovered Not yet recovered but improved Not yet recovered Unknown Fatal - Date of Death: _____

Severe? - Yes No Rechallenged? - No Yes Result: _____

OTHER FACTORS - Please tick or specify as appropriate

Renal disease Allergy : _____ Other Medical Conditions: _____

Hepatic disease Nutritional Suppl or OTC use : _____ Industrial Chemicals : _____

REPORTER - Please tick as appropriate: Doctor Pharmacist Dentist Nurse Other : _____

Name: _____

Address: _____

Signature: _____

Phone: _____ Date: _____

Send completed form to CARM

Freepost 112002, CARM, PO Box 913, Dunedin **or** Fax: (03) 479 7150



ADVERSE REACTIONS

What to report

Please report any suspect reaction of clinical concern. This includes adverse reactions involving:

- Prescription medicines
- Over-the-counter medicines (medicines purchased without a prescription)
- Complementary medicines (herbal medicines, naturopathic and/or homoeopathic medicines, and nutritional supplements such as vitamins and minerals)
- Vaccines.

In particular, please report the following:

- All suspected reactions to NEW medicines
- All events to IMMP medicines¹
- All Adverse Reactions of Current Concern²
- All suspected drug INTERACTIONS
- UNEXPECTED or SERIOUS reactions (including those suspected of causing death, admission to hospital, prolongation of hospitalisation, or birth defects)
- Serious ALLERGIC reactions (to enable a danger or warning to be entered in the national health database so re-exposure can be avoided for that individual).

How to report

Fill in the reporting form, which is available:

- overleaf (inside the back cover of *Prescriber Update*)
- from the CARM web site: <http://carm.otago.ac.nz/reporting.asp>

On-line reporting is also available on the CARM web site.

Where to report

Send all adverse reaction reports to CARM (Centre for Adverse Reactions Monitoring) in Dunedin.

Post to: Freepost 112002
 The Medical Assessor
 CARM
 NZ Pharmacovigilance Centre
 P O Box 913
 Dunedin

Fax: (03) 479 7150

Phone: (03) 479 7247

E-mail: carmnz@stonebow.otago.ac.nz

1. The list of medicines in the Intensive Medicines Monitoring Programme (IMMP) is on page 18

2. The list of *Adverse Reactions of Current Concern* is on page 17